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DOCUMENT-IDENTIFIER: US 5770624 A
TITLE: Certain alpha-substituted arylsulfonamido acetohydroxamic acids

Brief Summary Text (5):
The compounds of the invention are inhibitors of TNF-alpha converting enzyme (TNF-alpha convertase) and thus inhibit TNF alpha activity, e.g. suppress the production and/or release of TNF alpha, an important mediator of inflammation and tissue growth. Such properties render the compounds of the invention primarily useful for the treatment of tumors (malignant and non-malignant neoplasma) as well as of inflammatory conditions in mammals, e.g. for the treatment of arthritis (such as rheumatoid arthritis), septic shock, inflammatory bowel disease, Crohn's disease and the like.

Brief Summary Text (6):
The compounds of the invention also inhibit matrix degrading metalloproteinases such as gelatinase, stromelysin, collagenase, and macrophage metalloelastase. Thus the compounds of the invention inhibit matrix degradation and are also useful for the prevention or treatment of gelatinase-, stromelysin-, collagenase and macrophage metalloelastase-dependent pathological conditions in mammals. Such conditions include tumors (by inhibiting tumor growth, tumor metastasis, tumor progression or invasion and/or tumor angiogenesis), such tumors being e.g. breast, lung, bladder, colon, ovarian and skin cancer. Other conditions to be treated with the compounds of the invention include osteoarthritis, bronchial disorders (such as asthma by inhibiting the degradation of elastin), atherosclerotic conditions (by e.g. inhibiting rupture of atherosclerotic plaques), as well as acute coronary syndrome, heart attacks (cardiac ischemia), strokes (cerebral ischemias), restenosis after angioplasty, and also vascular ulcerations, ectasia and aneurysms.

Detailed Description Text (63):
Firstly, they are inhibitors of TNF-alpha converting enzyme CINF-alpha convertase) and thus inhibit TNF-alpha activity, e.g. suppress the production and/or release of TNF alpha, an important mediator of inflammation and tissue growth. Such properties render the compounds of the invention primarily useful for the treatment of tumors (malignant and non-malignant neoplasms) as well as of inflammatory conditions in mammals, e.g. for the treatment of arthritis (such as rheumatoid arthritis), septic shock, inflammatory bowel disease, Crohn's disease and the like.

Detailed Description Text (64):
Further, the compounds of the invention also inhibit matrix degrading metalloproteinase enzymes such as gelatinase, stromelysin, collagenase, and macrophage metalloelastase. Thus the compounds of the invention inhibit matrix degradation and are also useful for the treatment of gelatinase-, stromelysin-, collagenase- and macrophage metahoelastase-dependent pathological conditions in mammals. Such conditions include tumors (by inhibiting tumor growth, tumor metastasis, tumor progression or invasion and/or tumor angiogenesis), such tumors being e.g. breast, lung, bladder, colon, ovarian and skin cancer. Other conditions to be treated with the compounds of the invention include osteoarthritis, bronchial disorders (such as asthma by inhibiting the degradation of elastin), atherosclerotic conditions (by e.g. inhibiting rupture of atherosclerotic plaques), as well as acute coronary syndrome, heart attacks (cardiac ischemia), strokes (cerebral ischemias), and restenosis after angioplasty.

Detailed Description Text (69):

The above-cited properties are demonstrable in in vitro and in vivo tests, using advantageously mammals, e.g. rats, guinea pigs, dogs, rabbits, or isolated organs and tissues, as well as mammalian enzyme preparations. Said compounds can be applied in vitro in the form of solutions, e.g. preferably aqueous solutions, and in vivo either enterary or parenterally, advantageously orally, e.g. as a suspension or in aqueous solution. The dosage in vitro may range between about 10.sup.-5 molar and 10.sup.-10 molar concentrations. The dosage in vivo may range, depending on the route of administration, between about 0.1 and 100 mg/kg.

Detailed Description Text (84):
Stromelysin activity can also be determined using human aggrecan as a substrate. This assay allows the confirmation in-vitro that a compound can inhibit the action of stromelysin on its highly negatively-charged natural substrate, aggrecan (large aggregating prtoeoglycan). Within the cartilage, proteoglycan exists as an aggregate bound to hyaluronate. Human proteoglycan aggregated to hyaluronate is used as an enzyme substrate. The assay is set up in 96-well microtiter plates allowing rapid evaluation of compounds. The assay has three major steps:

Detailed Description Text (85):
1) Plates are coated with hyaluronate (human umbilical chord, 400 ug/ml), blocked with BSA (5 mg/ml), and then proteoglycan (human articular cartilage D1--chondroitinase ABC digested, 2 mg/ml) is bound to the hyaluronate. Plates are washed between each step.

Detailed Description Text (88):
Collagenase activity is determined as follows: ninety six-well, flat-bottom microtiter plates are first coated with bovine type I collagen (35 ug/well) over a two-day period at 30.degree. C. using a humidified and then dry atmosphere; plates are rinsed, air dried for 34 hours, sealed with Saran wrap and stored in a refrigerator. Human recombinant fibroblast collagenase and a test compound (or buffer) are added to wells (total volume =0.1 ml) and plates are incubated for 2 hours at 35.degree. C. under humidified conditions; the amount of collagenase used per well is that causing approximately 80% of maximal digestion of collagen. The incubation media are removed from the wells, which are then rinsed with buffer, followed by water. Coomasie blue stain is added to the wells for 25 minutes, removed, and wells are again rinsed with water. Sodium dodecyl sulfate (20% in 50% dimethylformamide in water) is added to solubilize the remaining stained collagen and the optical density at 570 nM wave length is measured. The decrease in optical density due to collagenase (from that of collagen without enzyme) is compared to the decrease in optical density due to the enzyme in the presence of test compound, and percent inhibition of enzyme activity is calculated. IC50's are determined from a range of concentrations of inhibitors (4-5 concentrations, each tested in triplicate), and K.sub.i values are calculated.

Detailed Description Text (94):
About 2 ng of recombinant truncated mouse macrophage metalloelastase (FASEB Journal Vol. 8, A151, 1994), purified by QSepharose column chromatography is incubated with test compounds at the desired concentrations in the presence of 5 mM CaCl.sub.2, 400 nM NaCl, [.sup.3 H]elastin (60,000 cpm/tube), and 20 mM Tris, pH 8.0, at 37.degree. C. overnight. The samples are spun in a microfuge centrifuge at 12,000 rpm for 15 minutes. An aliquot of the supernatant is counted in a scintillation counter to quantitate degraded [.sup.3 H]elastin. IC.sub.50 's are determined from a range of concentrations of the test compounds and the percent inhibition of enzyme activity obtained.

Detailed Description Text (97):
The effect on tumor angiogenesis can be determined e.g. in rats implanted with Walker 256 carcinoma in pellets to stimulate angiogenesis from vessels of the limbus, as described by Galardy et al, Cancer Res. 54,4715 (1994). The effect of the compounds of the invention on atherosclerotic conditions can be evaluated using atherosclerotic plaques from cholesterol-fed rabbits which contain activated matrix metalloproteinases as described by Sukhova et al, Circulation 90 I404 (1994). The inhibitory effect on matrix metalloproteinase enzyme activity in rabbit atherosclerotic plaques can be determined by in situ zymography, as described by Galis et al, J. Clin. Invest. 94, 2493 (1994), and is indicative of plaque stabilization (inhibition of plaque rupture).

Detailed Description Text (137):
The pharmaceutical compositions according to the invention are those suitable for eternal, such as oral or rectal, transdermal and parenteral administration to mammals, including man, to inhibit TNF-alpha converting enzyme and matrix-degrading metaloproteinases, and for the treatment of disorders responsive thereto, comprising an effective amount of a pharmacologically active compound of the invention, alone or in combination, with one or more pharmaceutically acceptable cartiers.

Detailed Description Text (145):
The present invention also relates to methods of using the compounds of the invention and their pharmaceutically acceptable salts, or pharmaceutical compositions thereof, in mammals for inhibiting TNF-alpha activity and inhibiting the matrix-degrading metalloproteinases, e.g. stromelysin, gelatinase, collagenase and macrophage metalloelastase, for inhibiting tissue matrix degradation, and for the treatment of TNF-alpha and matrix-degrading metalloproteinase dependent conditions as described herein, e.g. inflammation, rheumatoid arhritis, osteoatis, also tumors (tumor growth, metastasis, progression or invasion), pulmonary disorders, atherosclerosis and the like described herein. Tumors (carcinomas) include mammalian breast, lung, bladder, colon, prostate and ovarian cancer, and skin cancer, including melanoma and Kaposi's sarcoma.